

ANNOUNCEMENT
HISTORY
APPLICATION
REPORTS

Diphtheria
Antitoxic
Serum

H K MULFORD COMPANY
PHILADELPHIA
CHICAGO

FOURTH EDITION

:: :: Announcement :: ::

TO guarantee our patrons a thoroughly reliable *Diphtheria Antitoxic Serum*, at the earnest solicitation of many leading consultants, we established early in November, 1894, a complete Bacteriological Laboratory at 3907 to 3911 Egglesfield Street, (opposite Fairmount Park,) Philadelphia, under the direction of Dr. Joseph McFarland, Lecturer on Bacteriology in the Medical Department of the University of Pennsylvania.

We were the first firm in this country to establish a complete bacteriological laboratory for the production of Antitoxin. Our product is thoroughly tested, and we can guarantee a reliable and standard serum. Our claim for superiority over the various other antitoxins is supported by the fact that those physicians who have used the various serums report having received the promptest results from our product, and have noticed an absence of soreness at point of injection or urticaria which frequently follows the use of other antitoxins.

Our laboratory and stables are open to the inspection of the Medical Profession on the first Tuesday of each month, from 3 to 5.30 P. M., by request; cards being issued from our office on application.

H. K. MULFORD COMPANY.

Diphtheria Antitoxic Serum

THE method for the production of Antitoxic Serum depends upon the continuous and progressive introduction of a very powerful toxin into a mildly-susceptible animal, whose blood and tissues are thus stimulated to produce a neutralizing substance. Our method is as follows: From numerous cultures of the *bacillus diphtheriae* a particularly virulent one is chosen. To be very virulent $\frac{1}{2}$ ccm. of a twenty-four-hour-old bouillon culture should kill a 500 gramme guinea-pig in from twenty four to thirty-six hours. With this bacillus a number of tubes of alkaline peptone bouillon are inoculated and placed in the incubator. At the end of twenty-four to forty-eight hours the tubes are examined, and if found pure, the contents of each is carefully poured into a wide, flat flask containing about one litre of similar bouillon, and the flasks thus inoculated placed in the incubator until the growth is well established, and a sufficient amount of toxin distributed through the liquid; a matter accomplished in from two to six weeks. When sufficiently grown the cultures are examined microscopically to determine their purity, the bacteria they contain killed by the addition of 0.4 per cent. of trikresol, and filtered through porcelain so as to remove the dead bodies of the bacilli, which are irritating in character.

The strength of the toxin is estimated by injection into guinea-pigs, the desired strength being sufficient for 0.1 ccm. to kill a 500 gramme animal in 24 hours.

The only animal now employed is the horse, not that it furnishes any better serum than other animals, but because it can furnish the serum in larger amounts. BEFORE BEGINNING THE TREATMENT OUR HORSES ARE INVARIABLY TESTED FOR TUBERCULOSIS AND GLANDERS WITH TUBERCULIN AND MALLEIN. Much individual variation occurs among horses in their susceptibility to the action of the toxin, hence it is always well to begin the administration with a very small amount. We begin with 1.0 ccm. and repeat the injection about every eight days, according to the condition of the animal, doubling the amounts as often as possible, and as rapidly as possible ascending to the enormous amount of 300 ccm.

When the treatment has been kept up for three or four months, and the animals have reached the point at which they can stand the injection of 300 ccm. without other general or local symptoms than an œdema at the point of injection, they are ready to furnish Antitoxin of value.

The Antitoxin is in the serum of the blood. A trocar, with a canula attached to a rubber tube, is passed into the jugular vein of the animal, and the blood allowed to flow through the tube into sterile glass jars prepared to receive it.

The jars are stood upon ice, after the blood coagulates, for two days or more, until the serum, which separates, may be withdrawn by a pipette and placed in sterile receptacles.

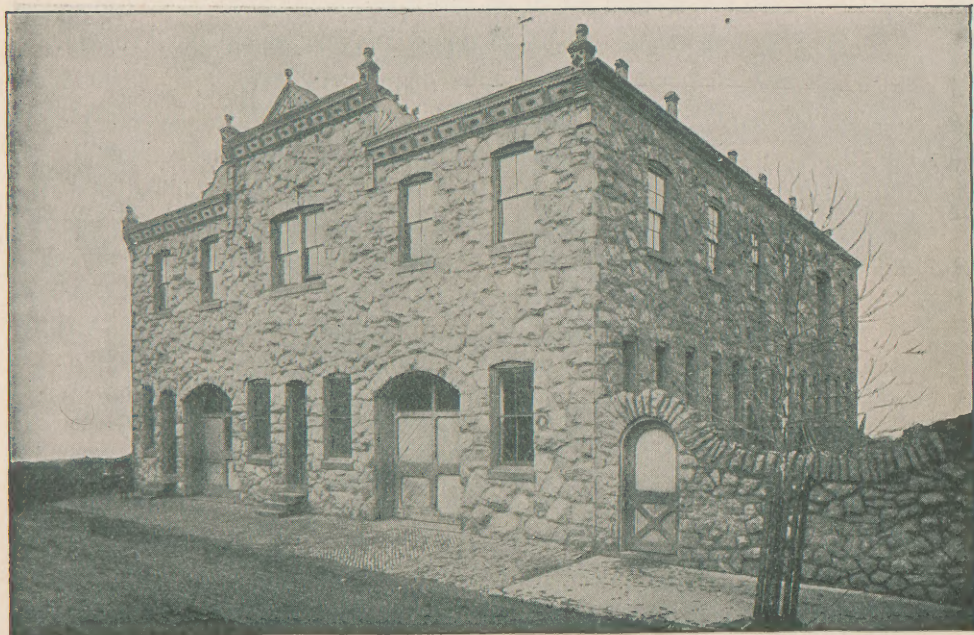
If properly carried out, without haste, the horse being kept in good condition, the power of the serum should be sufficient in an almost infinitesimal amount to protect a guinea-pig against a certain fatal dose of diphtheria toxin. When the serum is so strong that 0.1 ccm. of it will protect a guinea-pig against *ten times* the fatal dose of diphtheria toxin, it is called a *normal serum*, and contains one *immunizing unit* in the cubic centimetre.

Serums are described as normal, 10 times normal, 100 times normal, etc., meaning that relatively 0.1, 0.01, and 0.001 ccm. protect a guinea pig against the 10 times minimum fatal dose of the toxin.

The most desirable strength, and the one supplied by us, is the 100 times normal, which contains 100 immunizing units to the cubic centimetre.

By injecting the toxin into a vein, and carrying out the immunization for a longer period of time, a stronger antitoxic value—even 250 units per cubic centimetre, can be obtained. As, however, a severe urticaria occasionally follows the injection of such a serum into human beings, its use is less desirable than the standard as adopted by ourselves.

The serum is preserved by the addition of 0.4 per cent. of trikresol, which has proven most satisfactory, and is a feebly toxic agent. The trikresolized serum sometimes becomes fluorescent, even slightly opaque, but is not damaged by such a change, and the absence of putrefactive bacteria from such specimens can readily be determined by the microscope.



Biological Department

Biological Laboratory

H. K. Mulford Company



Biological Department

Bacteriological Laboratory

H. K. Mulford Company

While the serum does not retain its power indefinitely, we have tested our product after being preserved for ten months at ordinary temperature without obtaining evidence of deterioration or depreciation in its strength.

All the writers upon the theory of Antitoxin urge the necessity of using the material early in the course of the disease. *No case more than four days old is a satisfactory one for its trial, yet it may do good in any case*, and, being innocuous, should be employed in all doubtful cases while the bacteriological examinations are being made. If possible, the remedy should be employed within the first twenty-four hours, before the vitality of the patient is so depressed and his blood so completely poisoned as to prevent neutralization by the antidote.

It must be remembered that though the remedy is a specific, its function is to neutralize, or to bring about the neutralization of the toxin, not to regenerate destroyed tissues.

If the administration be delayed until the heart muscle is in a condition of fatty degeneration, the kidneys fatty and the nervous system disorganized, the Antitoxin is powerless, since it is *only specific for diphtheria*.

Mulford's Antitoxin will conform to all official requirements in that (a) it contains at the most but a slight sediment; (b) that a feebly toxic preservative (*trikresol*) be used in the proper proportion (*0.4 per cent.*); (c) that the serums have the date of preparation and strength expressed on label.

Our serum is a concentrated one, containing no inert or noxious substances, and to avoid confusion is prepared in but one strength.

No ill effects need be feared from our Antitoxic Serum. We have introduced 25 ccm. into a 6-pound rabbit without the production of a single symptom, although 10 ccm. of that amount was injected into the ear veins. Dr. Rosenthal reports a case of a child 8 years of age desperately ill, with most unfavorable prognosis, in which 14,000 units (140 c.c.) of our serum were injected within thirty-six hours, with curative result, and with no unfavorable symptom. The reported cases in which ill effects have seemed to follow the use of Antitoxin must be looked upon as simple coincidences.

Some have thought that the blood of the horse possessed, without any preliminary manipulation, a neutralizing property when brought in contact with the diphtheria toxin, but this is an error. *Normal horse serum does not contain a particle of protective substance, as our experiments and those of others have shown.*

Directions

DOSE.—The average dose for an infant up to 10 lbs. is 5 cc.* of the 100 times normal serum ; for a child of 10 to 25 lbs., 7 cc. ; for a child of 25 to 70 lbs., 10 cc. ; for a larger child or adult 10 cc. is an ordinary commencing dose. In proportion a seeming larger dose for children of small size is deemed necessary on account of their great susceptibility to the disease, and since the quantity of diphtheria toxin in the blood may be estimated to be as great as in larger children or adults. In ordinary cases a second injection should be given within from six to twelve hours if no improvement be noted.

WHERE THE DISEASE IS SEVERE, as manifested by the pulse, temperature, respiration and other constitutional symptoms, rather than by local manifestations, it is advisable that the ABOVE DOSES BE INCREASED BY ONE-HALF, and that a second injection be made in from four to eight hours of twice the ordinary dose. *Early and vigorous dosage is to be commended, since the best results with the Antitoxic Serum are secured where used in the first twenty-four to forty-eight hours of the disease, and since no ill results have been reported from over-dosage.*

Administration.—FIRST, ascertain with water if the syringe be in good working order. SECOND, sterilize the syringe thoroughly by boiling it for ten minutes; the needle and rubber tube being detached from each other and from the syringe, and the metal head of the syringe

*For those unaccustomed to the Metric System the following Table of Equivalents is of interest :

5cc. equals	80 min.	(1 1-3 fld. drachms.)
10cc. equals	160 min.	(2 2-3 fld. drachms.)
20cc. equals	320 min.	(5 2-5 fld. drachms.)

next to the handle unscrewed. (Caution is to be used in sterilizing the glass barrel, and it is best that it be placed in warm water and gradually brought to the boiling point.) THIRD, draw into the syringe the exact quantity of serum to be used. This can be most easily accomplished by attaching the needle to the rubber tube, fastening it to the syringe, taking care that all the water is ejected, and placing point of needle into the bottle of serum. Before making injection, see that all air is expelled from syringe.

Site for Injection.—The injections may be given wherever the skin is loose, between the scapulæ, near the hip, in the side of the abdomen, the latter being preferred, since this point is more free from pressure, while the patient is in bed. The site of the injection should be thoroughly scrubbed and cleansed with an antiseptic solution.

The injections *should be made slowly* into the subcutaneous or cellular tissue, the introduction continuing from three to five minutes, according to the amount, the absorption being much more rapid and the local disturbances much less than when the serum is forcibly injected. A rotary motion of the piston will aid in securing a slow steady flow.

After the injection a small quantity of absorbent cotton, which will become attached by the exudate, should be applied to the point of puncture, and will act as a protective.

Our serum is prepared in only one strength, each cubic centimetre containing 100 immunizing units. Bottles containing 5 cc. therefore contain 500 immunizing units, one immunizing dose, or an ordinary dose for a child up to 10 pounds weight. Bottles of 10 cc. contain 1000 immunizing units, or one curative dose for larger children or for adults. Bottles of 20 cc. contain 2000 immunizing units or two curative doses. We recommend, however, the purchase of vials containing 20 cc., since this permits a second injection of a curative dose, should the gravity of the disease require; and it may also be used for immunization.

Local Treatment.—The use of Diphtheria Antitoxic Serum does not warrant the neglect of other therapeutic measures; no one would think of neglecting the diet because the patient

was receiving an antidote for his blood poisoning, nor should the local lesions of the throat be neglected for the same reason, any more than one would neglect to dress an ulcer since the cause which had produced it was removed. Though Antitoxin is a specific for antagonizing the poison of the diphtheria bacilli, it must be remembered that it has probably no action on the streptococci or staphylococci which frequently are present in cases of true diphtheria. To destroy these pyogenic germs the physician may use any local treatment which he has by experience found of value, but we especially recommend the Toluol Solutions, which are prepared by us according to the formulæ of Prof. Loeffler, who discovered the bacilli of diphtheria, and whose experiments and clinical demonstrations prove these Toluol Solutions to be the most efficient means for local treatment, since they not only possess a vitally germicidal action on the bacilli of diphtheria, but kill the associated pyogenic organisms as well.

Numerous reports have been received from physicians who have employed our Toluol Solutions (Loeffler's) as a local application in acute follicular tonsillitis and pharyngeal inflammations, and the results are most satisfactory.

In pneumonia, and especially in diphtheria complicated with pneumonia, there is no remedy, as a local application, which will compare with these Toluol Solutions.

The reason for the local application and inhalation of the Loeffler's Solution is that we have found that it exerts a specific action on the *Fraenkel's diplo-coccus* (or *pneumono-coccus*).

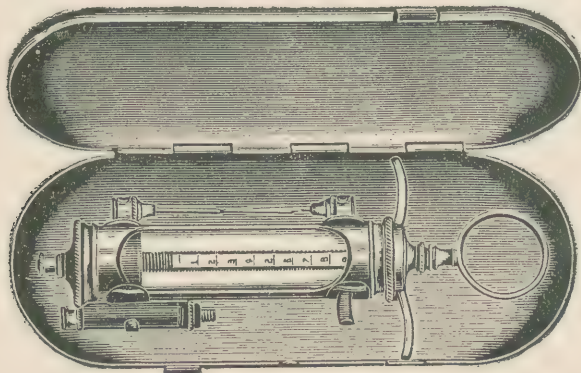
It is highly important that the throat and nasal passages be kept as free of mucus as possible ; for this purpose local applications by spray of our Benzo-Thymol Comp., or Hydrogen Peroxide diluted, will prove of exceptional value as an antiseptic and deodorant ; being non-toxic, they may be used freely.

In every case of supposed diphtheria we most strongly urge, as the only means of determining the true value of Antitoxic Serum, that a bacteriologic examination be made, Antitoxin being without effect on the non-diphtheritic anginas.

Syringe.—For the proper injection of the Diphtheria Antitoxic Serum we have designed a special syringe (see cut), which has many advantages over the article of foreign manufacture, which, beside being clumsy and unsatisfactory in practice, was packed in a wood or leather case, which could not be sterilized or rendered aseptic.

Our Improved Antitoxin Syringe is supplied in a metal case, and is so arranged that case and syringe may be thoroughly sterilized without injury. Another advantage is the soft rubber tube connecting the needle with the syringe, and permitting free movement of the body without danger of breaking the needle or causing pain to the patient. The packing being made of pure gum, is more satisfactory than asbestos, which we have discarded, since it becomes soft and pulpy. The syringe may be easily taken apart and sterilized by boiling.

Neatly packed, with two needles. Price, \$3.00.



R EPORTS which we have received from reliable physicians who have employed Mulford's Antitoxic Serum in over 1,000 cases of diphtheria, show a mortality of but 5.6 per cent. and in nearly every instance where the Serum treatment did not save the patient (due to the advanced state of the disease before the remedy was employed) the symptoms were greatly relieved. **In no cases were any unfavorable results noted.**

We confidently believe if the Serum is promptly employed in the first 24 to 48 hours, a mortality not greater than 3 to 4 per cent. will be shown.

Order at once, so that prompt treatment may be given your patients.

WE HEREWITH APPEND A FEW OF THE REPORTS RECEIVED.

H. K. MULFORD COMPANY.

Philadelphia, July 15th, 1895.

Dear Sirs:—I have treated 4 cases of Diphtheria with your Antitoxin Serum each case being verified by a bacteriologic examination from the Philadelphia Board of Health's Laboratory, Diphtheria Bacilli were found in all . . . at present each of these cases is reported well and out in the streets at play with other children; a bacteriologic after examination (after the fauces were clean again) proving the absence of the Diphtheria Bacilli.

Yours respectfully,

SAMUEL P. GERHARD, M.D., 639 N. 16th St.

H. K. MULFORD COMPANY, Philadelphia, Pa.

St. Louis, Mo., July 28th, 1895.

Gentlemen:—Have used Behring's and Mulford's Antitoxic Serum and find one as efficient as the other. Of late have only used Mulford's, as I could get it quickly and fresh, and have so far treated some 20 cases of Diphtheria and Diphtheritic Croup, and have had no fatal results.

Have used it in a baby of 16 months and another of 20 months, also in adults. Have seen no bad results from it so far. Am of course very careful to have syringe, needles, and skin aseptic. I fully believe that the Serum if used early is a specific, but would also advise local treatment with stimulants, etc.

Yours very truly,

EUGENE F. HAUCK, M.D., 1638 S. Jefferson Ave.

MESSRS. H. K. MULFORD COMPANY.

Philadelphia, September 15th, 1895.

Gentlemen:—* * * * * I have used your Antitoxin in 8 cases, and all successful. Am very enthusiastic over it.

Yours,

J. NEWTON SNIVELY, M.D., 2501 Oxford St.

H. K. MULFORD COMPANY.

Philadelphia, Pa., August 13th, 1895.

Gentlemen:—I have treated 72 cases of Diphtheria in this city with Antitoxin (H. K. Mulford Co.'s) with highly satisfactory results; prompt and complete recovery in all cases. Bacteriologic examinations were made by the Philadelphia Board of Health. I have used immunization in over 200 instances and in no case was Diphtheria contracted, although patients were frequently in the room with the contagion. . . I have found your Serum equally as efficacious as the foreign product, and shall continue using it.

517 Pine St.

EDWIN ROSENTHAL, M.D., Philadelphia.

TO H. K. MULFORD CO.

Waterloo, Ia., September 21st, 1895.

Gentlemen :—Some time since I procured a quantity of Antitoxin from your house, and provided our local physicians with the same for use in our Diphtheria epidemic. Without exception these physicians now commend its use, and this in spite of the fact that most were somewhat skeptical of the matter. It is also a fact that while the Antitoxin was usually resorted to as a last resource, after ordinary measures were considered useless, the wonderful results made converts of us all, and again would be used in every case the moment the true diphtheritic nature of the disease was ascertained.

The Mulford product gave the best of results and was found perfectly reliable. In no case was there the slightest ill-effects of the treatment and the progress of the disease was invariably checked, and only in those cases where the blood had become so charged with the poison that elimination was no longer possible, did death ensue.

Our epidemic numbered 70 cases with 4 deaths. I am confident had Antitoxin been used early, not over one of the four would have died.

I am, very truly,

C. F. BENNETT, Health Officer,
City of Waterloo.

H. K. MULFORD COMPANY, Philadelphia, Pa.

Akron, O., June 4th, 1895.

Gentlemen :—I have treated 34 cases of Diphtheria in this city with Antitoxin (H. K. Mulford Co.'s) with but two deaths, and one of those cases had been sick 10 days before I saw it, so that it should not be counted in the statistics.

L. S. EBRIGHT, Health Officer.

H. K. MULFORD COMPANY.

Haddonfield, N. J., July 12th, 1895.

Dear Sirs :—I have used your Antitoxin in an infant 6 weeks and 3 days old, with marked pharyngeal, tonsillar and nasal patches. The child could not nurse for 2 weeks, and for over 1 week was fed small quantities of milk with a little whisky every hour or two; could not accept more than 3 teaspoonfuls at each feeding. Your Antitoxin worked most successfully, and through it I attribute the child's recovery.

The mother also developed Diphtheria, as well as the sister 3 years and 3 months old, all improved greatly and cases terminated successfully, after the use of Antitoxin

Yours very truly,

W. S. LONG, M.D.

H. K. MULFORD COMPANY.

Falsington, Pa., August 2d, 1895.

Dear Sirs :—Although my experience in the treatment of Diphtheria with Antitoxin is limited, I am free to confess that the experience which I have had with the Serum treatment is such that I would not feel that I had done my duty with my patient suffering with Diphtheria if I did not give to him the benefit of the treatment of Antitoxin.

Yours very truly,

J. N. RICHARDS, M.D.

H. K. MULFORD COMPANY.

Red Wing, Minn., August 13th, 1895.

Gentlemen :—I have used your Antitoxin in 9 cases, and am pleased to report complete recovery in each case. I have also used Antitoxin as an immunizing agent in 16 cases, and have not had a single patient to contract the disease after the immunizing dose was administered. Shall continue to use Antitoxin.

Very truly yours,

CORYDON FARRAND, M.D.



Biological Department

Injecting the Toxin

H. K. Mulford Company



Biological Department

Drawing Blood from Immunized Horse

H. K. Mulford Company

Discussion on Diphtheria Antitoxic Serum.

Philadelphia County Medical Society, September 11, 1895.

DR. EDWIN ROSENTHAL: I would only add to the discussion one remark, and that is that I think there is no necessity of sending abroad now for antitoxin, when serum of equal value can be obtained in this city. I have seen but two fatal cases in this method of treatment, and in both Behring's serum was employed. In all the cases in which Mulford's antitoxin was used, under my observation, the results were successful. * * * * * I am speaking only of what has come under my own observation, and not to condemn the imported serum. I merely wish to state that the results of the American preparation have been perfectly satisfactory in my hands, as well as in the hands of others.

With regard to the value of this method of treatment of diphtheria I can only say that my faith in it is such that if I were called to treat a case, and could not get the antitoxin, I should be very much at a loss indeed; for then I would have to contemplate what was before the sufferer—the days and nights of ceaseless vigil and work, and then the result always dubious. And with antitoxin: how the duration of the disease is shortened, how relief is quickly obtained, and the gratifying results. Again, where immunization is practiced it takes away the dread of the disease from those in attendance, and the relief to the minds of such individuals cannot be estimated.

When intubation is practiced the tube can be withdrawn in a much shorter time than without this treatment, and we can almost speak with certainty of the day when this is done. This is of great importance, especially when we are called into country districts or where the patient lives at a distance, because visits are necessary, and the sooner the case is over the better. I recollect one case in the practice of Dr. Frank T. Anderson, at Paschallville, where the tube was withdrawn and reinserted for twenty-eight days; this was during the time when antitoxin was unknown. The distance from my home was probably eight miles, and necessitated a number of visits. Since the antitoxin period I visited a case with Dr. Anderson in the same section of this city, and in three days my attention ceased. So in other cases; and for that reason I always reiterate, that in laryngeal diphtheria antitoxin is specifically indicated, and its marvelous value can here be proven.

Report.

THE need of the early application of the remedy is shown by Dr. Foster in *The Medical News* of February 2, 1895, who reports 2740 cases collected from all sources treated by Antitoxin with a mortality of 18.54 per cent., but "that all cases recovered in which the Antitoxin treatment was begun on the first day of the disease; that 2.83 per cent. of the cases died in which it was begun on the second day; that 9.99 per cent. of the cases died in which it was begun on the third day; that 20 per cent. of the cases died in which it was begun on the fourth day; that 33.33 per cent. of the cases died in which it was begun on the fifth day; and that 41.38 per cent. of the cases died in which it was begun after the fifth day."

Professor Virchow, of Berlin, who pointed out the demerits of tuberculin in the treatment of tuberculosis, who has always decried the germ theory of disease, and who does not believe that the Klebs-Löffler bacillus is the cause of diphtheria, in an argument, upon the value of diphtheria antitoxic serum, with von Bergmann (see *Med. Record*, Jan. 12, 1895) made the following interesting communication:

"Treatment by diphtheria antitoxin was begun last March in the Kaiser and Kaiserin Friedrich's Hospital. In June and July nearly all diphtheria cases were treated with the serum. The results were as follows:

First week, cured 13; deaths, 1 child.	Sixth week, cured 1; deaths, 1 child.
Second " 9 " 1 "	Seventh " 3 " 0 "
Third " 6 " 2 children.	Eighth " 5 " 0 "
Fourth " 12 " 1 child.	— —
Fifth " 6 " 2 children.	55 cured. 8 deaths.

Suddenly the supply of serum ceased, as, unfortunately, the very horses from which the serum was taken died. The old methods of diphtheria treatment had again to be resorted to, and the results were:

First week, cured	5	deaths,	7 children.	Sixth week, cured	8	deaths,	12 children.
Second " "	6	" "	8 " "	Seventh " "	13	" "	6 " "
Third " "	6	" "	6 " "		—		—
Fourth " "	8	" "	11 " "		54	cured.	54 deaths.
Fifth " "	8	" "	5 " "				

This sad increase in the mortality induced the hospital to return to the serum, which was then procured from Höchst. Immediately there was a change:

First week, cured	3	deaths,	2 children.	Fifth week, cured	17	deaths,	1 child.
Second " "	4	" "	1 child.	Sixth " "	17	" "	5 children.
Third " "	14	" "	1 " "		—		—
Fourth " "	14	" "	2 children.		69	cured.	12 deaths.

The total figures were as follows: In the whole space of time 533 cases were treated—303 with the serum, 230 without. The former had 13.2 per cent. of deaths; the latter 47.8. Virchow continued that, in view of these results, he held it to be the duty of every doctor to use the serum in diphtheria. "All theoretical considerations," he added, "must give away to the brute force of these figures." He continued that, even if disagreeable by-effects were proved to occur here and there, they were not sufficient to dissuade him from continuing the treatment.

Roux (*Brit. Med. Jour.*, No. 1757) reports that in l'Hôpital des Enfants the mortality for four years was 51.71 per cent. In the six months since antitoxin was used 448 cases gave 24.5 per cent. of mortality, and during same six months, in Trousseau Hospital, without antitoxin, 60 per cent. died.

Ganghofer (*Prager Med. Woch.*, 1895, Nos. 1, 2, 3) reports that in Kaiser Franz Josef Children's Hospital, of 110 cases given antitoxin, 12.7 per cent. died, while in the intervals of the treatment and immediately preceding, 43 per cent. was the mortality rate.

Sonnenberg (*Deut. Med. Woch.*, 1894, No. 50) reports that the serum was used in Moabit Hospital for five months with two intermissions, during which no serum could be had. In the intermissions 116 cases were treated with death rate 27.6 per cent., 40.5 per cent. required tracheotomies, and of these 38 per cent. died. When antitoxin was available, 107 cases were treated, with death rate of 20.6 *per cent.* The per cent. requiring tracheotomy was 31.8, and of these 25.5 per cent. died.

Prof. Kolisko (*British Medical Journal*, No. 1781), having had an experience of one thousand post-mortem examinations of diphtheria cases during the last twelve years, and seventy-five upon those dying after antitoxic treatment, found the diphtheritic membrane much more loosely attached to the mucous membrane in the latter cases than was usual. He found the kidney changes were the same as before its use.

Katz (*Berl. klin. Woch.*, July 16th, 1894) says, that in the Kaiser and Kaiserin Friedrich's Kinder Krankenhaus the death rate from 1890 till the serum therapy was introduced varied in the different years from 32.5 to 50.4 per cent. Since then 128 cases, confirmed by bacteriologic examination, showed only 16.5 per cent. mortality.

Bokai (*Lancet*, No. 3714) compares a mortality for the month of October in 1891, 1892 and 1893, of 56.8, 42.9 and 61.7 per cent., respectively, with that of 1894 of 14.33 *per cent.* of cases in the Budapesth Stephanie Hospital for Children.

Dr. Peral, Pathologist to the Trieste Municipal Hospital, performed in the last three months eighty-two necropsies on persons dead of diphtheria, thirty of whom had been given antitoxic treatment. In these latter he found the trachea free from diphtheritic membrane, while in the majority of the others it continued from the fauces to the trachea. He could tell from the appearances, post-mortem, whether or not antitoxic serum had been the treatment.

Excerpts from the Treatment of Diphtheria by Antitoxin.*

The laboratory does not furnish any more impressive experiments than those which demonstrate the power of antitoxic serum to prevent and to cure the disease caused in animals by inoculation with the diphtheria bacillus or its poison. The serum arrests the spread of the local process and abates the symptoms of general toxæmia. These experiments prove beyond question that this healing serum possesses properties which are directly and powerfully antagonistic to the toxic action of the diphtheria bacillus, and there is no good reason to doubt that under similar circumstances this antagonistic power, so readily and surely and uniformly demonstrable in the case of lower animals, will manifest itself also in human beings. The only question, and that of course an important one, in this connection is: To what extent the conditions in the treatment of experimental diphtheria by antitoxin are or can be made similar to those in the therapeutic application of the same agent to human diphtheria?

We have no certain knowledge as to the nature of the substances called antitoxins nor as to their mode of action. This is not, however, an argument against their therapeutic employment, for we have no positive knowledge as to the mode of action of many of our therapeutic agents. [For example, the tonic action of quinine and the alterative action of arsenic and the mercurials.]

There are two prominent theories as to the mode of action of the diphtheria antitoxin. The one may be called the chemical and the other the vital theory. The chemical theory is that the antitoxin directly neutralizes in a chemical sense the toxins. This seemed to be the natural interpretation of the fact that the injection into susceptible animals of a mixture in suitable proportion of the antitoxin and the toxin is harmless, but Buchner and Roux have shown that this earlier view is incorrect, and that by selecting animals of greater susceptibility or by increasing the natural susceptibility of an animal, the presence of active

* By WILLIAM M. WELCH, M.D., *Pathologist to the Johns Hopkins Hospital and Professor of Pathology, Johns Hopkins University.* See *Bulletin of the Johns Hopkins University Hospital*, July-August, 1895.

toxin in the mixture can still be demonstrated. The experimental evidence, therefore, is in favor of the other theory, *viz.* : that the antitoxin acts through the agency of the living body, and probably in the sense that it renders the cells tolerant of the toxin.

The results of the treatment of human diphtheria with antitoxin speak also in favor of this vital theory.

If, as seems probable, the curative effects of the healing serum are brought about through the agency of the living cells of the body, we can understand why these effects will not follow the introduction of the serum with the certainty and precision of a chemical reaction. The cells must be in a condition to respond in the proper way to the introduction of the antitoxic serum. For one reason or another this responsive power may be in abeyance. It may be weakened by intense or prolonged action of the diphtheria poisons, or by other previous or co-existent disease, or by inherent weakness, or there may even be some individual idiosyncrasy which hinders the customary response of the cells to the antitoxin. Clinical experience shows that cases of diphtheria inherently refractory to timely treatment with antitoxic serum are most exceptional, if indeed they occur at all.

The general rules regarding the dosage of antitoxin are sufficiently well known not to require mention here, and I speak of this matter only to indicate that because a patient may have received a dose or even two or more doses of antitoxin, this furnishes no absolute guarantee that a quantity of antitoxin adequate to neutralize the effects of the toxin has been given. We now know that in the early period following introduction of the treatment entirely insufficient doses were given.

Both experiments on animals and clinical experience demonstrate that the earlier antitoxic serum is administered after the inception of the disease, the better are the chances of recovery. It is usually impossible to rescue the lives of guinea-pigs by means of antitoxin if the treatment is delayed longer than forty-eight hours after inoculation with an amount of diphtheria

poison fatal to these animals in four or five days, although the duration of life may be considerably prolonged. In human beings the conditions are different, but the evidence is conclusive that the superiority of the serum treatment over all other methods is most strikingly manifested in the results of the cases in which the antitoxin is given not later than the third day of the disease. Although in many cases the treatment is beneficial when the antitoxin is administered in *larger* doses at a *later* period of the disease, the importance of beginning the treatment at the earliest possible date, without waiting to determine by cultures whether or not the Löffler bacillus is present, cannot be too strongly emphasized.

Without doubt the remedial rôle of diphtheria antitoxin is materially restricted by its inability to combat developed streptococcus sepsis, broncho-pneumonia and other complications referable to secondary infection, or to stop impending suffocation by immediate removal of mechanical obstacles in the form of false membranes in the air passages, but the antitoxic serum is the most powerful agent which we possess to prevent the development of these complications and secondary infections. The timely administration of the healing serum, by antagonizing the effects of the Löffler bacillus, antagonizes in large part the causes of the increased susceptibility to secondary infections, and thus lessens the frequency of their occurrence.

In considering the obstacles in the way of cure of diphtheria by antitoxin, the self-evident fact should not be forgotten that this remedy cannot restore cell life which has already been seriously damaged by the action of the diphtheria bacillus or its poison. The researches of Oertel upon human diphtheria, and those of Flexner and myself upon experimental diphtheria, demonstrate that the toxins of the diphtheria bacillus are most powerful poisoners of cells, the internal lesions of pure diphtheria being especially characterized by widely distributed areas of cell death. We have no way of gauging accurately, at any given period of the disease, the extent of the damage already inflicted upon the cells of the body. If the nerve cells or their axis cylinders have already been so damaged that paralysis must follow, or the cardiac nerve

cells or muscular fibres have been similarly injured, or the renal epithelium so affected that degeneration and nephritis ensue, the administration of antitoxin cannot restore these cells which are already on the way to degeneration and death.

This irretrievable damage to cell life may be present for a considerable time before we are able to recognize its effects. P. Meyer detected pathological changes in the peripheral nerves as early as the third day after the onset of diphtheria and before paralysis was manifest. The occurrence of paralyses, including cardiac paralysis, after antitoxin had been administered even thus early in the disease, cannot therefore necessarily be attributed to failure of this agent to neutralize toxin developed after its injection.

Antitoxic serum is a new and strange remedy, but the effects which follow its injection in individual cases are not new and strange. Nothing happens which the physician may not have occasionally seen to happen in cases treated in the ordinary way. In severe as well as in mild cases of diphtheria he may have seen an apparently progressive local process quickly arrested and the general symptoms promptly abated. But why should anything new and strange happen after the administration of antitoxin? Cure by antitoxin is cure by nature's own remedial agent. That which is new and strange is the frequency with which, in case after case, the timely injection of antitoxin promptly arrests the local inflammation and checks the constitutional disturbance.

Recovery following treatment by antitoxin is such a natural kind of recovery that in any given case the physician may readily have the feeling that the same thing might have happened without the use of the remedy. We can, therefore, understand why it should be those with the largest experience in the treatment of diphtheria by antitoxin who are most decided in expressing their opinion as to its beneficial effects. The very fact that the mode of cure is such a natural one, and unattended by peculiar phenomena, is an obstacle to drawing positive conclusions from a small number of observations, even if these appear to be most favorable.

That there should be wide diversity in the percentage of cures in reports of different observers is, of course, to be expected when we consider the varied character of the cases treated and the importance of early administration of antitoxin. It may happen that a series of cases is made up so largely of advanced and complicated diphtherias at the time when the antitoxic treatment is begun, that the beneficial effects of the treatment are not apparent. It is, on the whole, remarkable that there should have been so few reports in which the fatality has not been materially diminished during the period of administration of antitoxin.

So far as the testimony of physicians based upon their clinical experience is concerned, this is overwhelmingly in favor of the antitoxic treatment, wherever their experience in its employment has been a large one ; those with less experience are often even more enthusiastic.

It is scarcely ten months since antitoxin has been used by more than a very few favored physicians, and it is a much shorter time since its use has become at all general. In this comparatively short time there have, however, been published more or less definite reports of the results of the treatment in at least 15,000 cases. These are presented as by no means complete, only the more readily accessible journals have been consulted, but it is believed to include all of the more important reports. Nor has use been made of such merely general published statements without detail as that there have been treated in France up to the end of December, 2,700 cases with a mortality of 16 per cent. ; in Austria, outside of Vienna, 950 cases with a mortality of 15.7 per cent. ; in Croatia and Slavonia, 428 cases, with a mortality of 10.8 per cent. ; in Berlin Hospitals, 1,500 cases, with a reduction in fatality of one-half, etc.

What are the objections which may be and have been urged against this natural interpretation of the statistical evidence? In the first place it has been claimed that these observations have been made during the prevalence of unusually mild diphtheria. In some places the prevailing type of the disease seems to have been mild, but the great majority of the observers quoted in the table consider that the prevailing diphtheria in their localities has been of average

severity, and they cite in many instances the 'simultaneous fatality of cases not treated with antitoxin as proof that the disease is not of peculiarly mild type, indeed in several places it seems to have been of more than average severity. During the period in which Roux treated with antitoxin 300 cases in the Hôpital des Enfants-Malades with a fatality of 26 per cent., the fatality in the Hôpital Trousseau, also in Paris, receiving a similar class of cases, was 60 per cent.

So far, no proof has been brought forward in support of the opinion that the low percentage of fatality of diphtheria treated with antitoxin can be referred in any large measure to the prevalence of an unusually mild type of the disease, although in a few scattered groups of cases, particularly some of the smaller series in my table, this may be in part the explanation.

It is manifestly improper to compare the average fatality of thousands of cases treated in hospitals with antitoxin with exceptionally favorable results at certain periods in a few hospitals in a comparatively small number of cases without serum treatment, and still more improper, as has even been done, to make such comparison with the most favorable percentages which one can find reported from private practice or in municipal mortality statistics. Surely some consideration must be given to the previous and simultaneous results obtained from cases without serum treatment in the same hospitals from which the cases reported are derived.

It is interesting to learn that in Boston during the antitoxin period (January 1 to May 1, 1895), the total fatality from diphtheria was 14 per cent., as compared with a fatality of 31 per cent. during the corresponding period of previous years (Mason), and that in Cartagena, Spain, during four months of employment of antitoxin, the total number of deaths was only one quarter the average number for the same period of time during the preceding ten years.

Risel reports the results in all of the cases treated by antitoxin during two months in the city of Halle. They are derived from the practice of thirty physicians among the poor and the rich, in the houses of the patients and in hospitals, and include mild and severe cases as

they presented themselves. Of the 89 patients treated in their homes, almost without exception children not over 7 years of age, 6 died, giving a fatality of 6.7 per cent. 19 of these had laryngeal diphtheria, of whom 4 died. Of the 25 patients treated in hospitals, 3 died, a fatality of 12 per cent. 15 of these had laryngeal involvement, of whom 3 died. The total fatality was 7.9 per cent.

A most convincing demonstration of the healing power of antitoxin is furnished by the experience of Baginsky during an involuntary pause in the serum treatment caused by failure in the supply of serum. Between March 15th, 1894, and March 15th, 1895, there were treated in Baginsky's service by antitoxin 525 children with a fatality of 15.6 per cent. During the period of forced interruption of the serum treatment, this period being chiefly the months of August and September, 126 children were treated without antitoxin, with a fatality of 48.4 per cent. There was absolutely no selection of cases in either group. In his comments upon this experience Baginsky says: "It is all the more remarkable, as the ratio of mortality of those treated with the serum both before and after the period of interruption varied within very small percentage figures. If one will permit figures to speak at all, there has scarcely been made on human beings a more demonstrative test of the curative power of a therapeutic agent. It was an experiment forced upon us, but it proved how terrible was the form of disease which we were treating, and how numerous would have been the victims without the use of the healing serum."

A similar experience has been reported by several other writers. Thus Körte noted a rise in fatality from 33.1 per cent. during the serum period to 53.8 during the period of failure in the supply of serum. Ganghofner, under similar conditions, a rise from 12.7 per cent. to 53.2 per cent.; Heim, from 22 per cent. to 65.6 per cent., and during the epidemic in Trieste the fatality rose from 18.7 per cent. to 50 per cent., when the serum failed. All of these highly significant observations were made on cases occurring in the same epidemic, the period of enforced interruption of the serum treatment being preceded and followed by the periods of serum treatment.



From Biological Department

Horses Immunized against Diphtheria Toxin

H. K. Mulford Company

We have considered thus far mainly the hospital statistics. These are for manifest reasons more numerous, larger and more carefully analyzed than those from private practice. It is, however, in private practice, especially among those classes who are in the habit of calling the physician early in the disease, that the best results from serum treatment are to be expected, for here there is more frequent opportunity for timely treatment.

Most noteworthy has been the improvement in the results of serum therapy of diphtheria in the Paris hospitals since Roux's original communication to the Congress in Budapest in September, 1894. The fatality has descended from Roux's original percentage of 26, in the later reports, to 14.7, 12 and 10 per cent., and according to a recent statement of Moizard and Bouchard (July, 1895), it at present oscillates between 8 and 14 per cent. These are the best results which have hitherto been reported from any hospital for any large number of cases, and they are certainly most significant. As Moizard and Bouchard in their recent communication say, "This result can no longer be attributed to fortunate series of cases, as was claimed at the beginning by adversaries of the method. Thousands of patients have been treated, and it can now be said that the controversy is closed."

No one can claim that laryngeal diphtheria requiring intubation or tracheotomy is anything but a severe disease. If the benefits of antitoxin are unmistakably manifested in these operated cases of croup, then the test is an *experimentum crucis* and puts an end to the objections of those who assert that the apparently favorable results of serum therapy in diphtheria are attributable mainly to the large proportion of mild cases treated.

Of the cases reported 27.2 per cent. required tracheotomy or intubation. There were, however, many more cases of laryngeal diphtheria in this group than the ratio of operative cases would indicate, for it is the testimony of the great majority of the observers that the stenotic symptoms of laryngo-tracheal diphtheria are relieved without the necessity of operation in a much larger proportion of the cases treated with antitoxin than by any other method

of treatment. As is well known, recovery without intubation or tracheotomy from descending laryngo-tracheal diphtheria, especially in children, is exceptional under all other methods of treatment, and the greater relative frequency with which such recovery occurs under serum treatment is a strong proof of the efficacy of antitoxin.

To-day in the presence of a child with dyspnœa it is not necessary to press for operation. One can inject the serum and wait as long as possible. Since the introduction of the serum the number of tracheotomies in the pavilion has diminished.

Out of his large experience Baginsky expresses himself in these vigorous words: "Here again the observation of the individual cases of laryngeal stenosis, and more especially of those which do not come to the point of operation, speak to me more forcibly than the statistical figures. The surprising regression of the laryngo-stenotic respiratory phenomena, the freedom of breathing, the disappearance of the hoarse voice and the croupy cough, the euphoria of the children, the change in their general condition, so that two days after the injection they are sitting up in bed, playing and contented and observant of their surroundings; all of these things produce in him who has had before his eyes for years the hopeless picture of continually progressing laryngeal stenosis, in very truth ineffaceable impressions."

It is this power of antitoxin to check the spread of the diphtheritic process from the tonsils and pharynx into the larynx, and from the larynx into the bronchi, which has impressed many observers in favor of the new treatment more forcibly than any other feature of their experience with its action. Thus Vierordt observed that of 24 children with diphtheria who were admitted with unaffected larynx and treated with antitoxin, only one developed temporarily a hoarse cough on the third day. In all of the others the larynx remained free. Of 23 patients who were admitted with unaffected larynx not long before the introduction of the serum treatment, nine afterwards developed croup. This is doubtless a somewhat unusual experience as regards the large proportion of cases of croup developing under previous methods of treatment.

An agent which would arrest the progressive descent of the diphtheritic process from the larynx into the bronchi and hasten the disappearance of the obstructive exudate is just what was needed to make intubation the ideal operation for the relief of the great majority of cases of croup requiring operative interference. Such an agent we now possess in antitoxin for a large group of cases, and we are not surprised, therefore, to find that the employment of intubation, as a substitute for tracheotomy, has been greatly extended by the introduction of serum therapy.

The following table is the summary of 19 reports, in which the number of the cases, with the results corresponding to the disease on which antitoxin treatment was begun, is given for each day up to and after the 6th day :

19 Reports.	Total.	1st Day.	2d Day.	3d Day.	4th Day.	5th Day.	6th Day.	After 6th Day.	Undetermined.
Cases.....	1489	222	456	311	168	116	44	104	(68)
Deaths	212	5	37	42	32	34	15	35	(12)
Percentages	14.2	2.2	8.1	13.5	19	29.3	34.1	33.7	(17.6)

Including in the 19 reports those of Schroeder, Blumenfeld and Rapmund, we have the following table, which gives the results of antitoxin treatment begun on the 1st and 2d, on the 3d and 4th, and after the 4th day :

22 Reports.	Total.	1st and 2d Day.	3d and 4th Day.	After 4th Day.	Undetermined.
Cases.....	1702	814	534	286	(68)
Deaths.....	229	45	81	91	(12)
Percentages.....	13.5	5.5	15.2	31.8	(17.6)

It may also be computed from the table that of 1729 cases of diphtheria with a fatality of 14.9 per cent., 1115 cases treated with antitoxin during the first three days of the disease yielded a fatality of 8.5 per cent., whereas 546 cases in which antitoxin was first injected after the 3d day of the disease yielded a fatality of 27.8 per cent. Of 232 cases in which treatment was begun on the 1st day, 5 (2.15 per cent.) died. Of 492 cases in which treatment was begun on the 2d day, 38 (7.7 per cent.) died. Of 331 cases in which treatment was begun on the 3d day, 43 (13 per cent.) died.

It is noteworthy that the percentage of deaths in 814 cases in which treatment was begun before the 3d day of the disease is only 5.5. If the doubtful deaths attributed to the 1st day be excluded, the percentage actually falls a trifle short of 5. If we furthermore make allowance for the fact that the assigned duration of the disease can scarcely be shorter, but may readily be longer, than the actual duration, then our tabulation of 1702 cases of diphtheria according to the day of beginning treatment verifies Behring's original prediction. I do not, however, consider that it is justifiable from so small a number of cases, and from material of the kind composing our table, to draw any definite conclusions as to the exact percentages of deaths according to the date of beginning treatment.

According to the table the percentage of deaths in cases in which the serum treatment is begun on the third and fourth days of the disease is nearly three times greater than that in cases treated on the first and second day, and the percentage after the third day is three-and-one-quarter times greater than that of cases treated within the first three days.

We are, of course, not to infer from these results that antitoxin may not be beneficial when administered after the 3d or 4th day of the disease. There are cases which are still mild after this duration, but which subsequently become serious, and even in desperate cases antitoxin holds out some hope of cure.

In the favorable cases the local diphtheritic process is arrested, usually within the first

twenty-four hours after the injection. Membrane may appear upon spots previously inflamed and invaded by the bacilli, but otherwise there is no extension of the membrane in the majority of the cases which are benefited. The area covered by membrane becomes sharply demarcated and the swelling of adjacent mucous membrane disappears. The membrane may disappear by rapid separation or by gradual softening. Sometimes it persists for several days after disappearance of all other local disturbance. Large membranous casts are coughed up from the larynx, trachea and bronchi under the serum treatment more frequently than under former methods. The rapid separation of the membrane in the lower air passages may cause sudden increase of stenotic symptoms. Nasal discharge is lessened. The swelling of the glands in the neck and the surrounding cedema disappear, so far as these are not referable to secondary infections.

The most uncertainty prevails as to the influence of antitoxin in preventing the three most important complications or sequelæ of diphtheria, nephritis, heart failure and paralysis. The weight of evidence is that genuine nephritis is far less common in cases treated by antitoxin sufficiently early than under other methods of treatment, but it is questionable whether albuminuria is less common, although it is considered to be by Kossel, Roux and others. If there is an albuminuria in any way directly referable to the injection of the serum, and this is by no means established, it is simple albuminuria with perhaps a few narrow hyaline casts but without evidence of any serious damage to the kidney. Peptonuria, it is claimed by Hecker, is an effect of the serum, but it is without clinical significance. Albuminuria is such an extremely common symptom of diphtheria that it must be very difficult to determine that it can be referred to the serum in any case.

It is apparent from what has been said that antitoxin is most strikingly beneficial in progressive fibrinous diphtheria, and especially in the prevention and cure of laryngeal diphtheria. In septic diphtheria the serum treatment is of little avail.

There have been a few cases reported in which the writers, without any satisfactory evidence whatever, have referred the death of the patient to the use of the serum. The essential harmlessness of the serum has been demonstrated by over two hundred thousand injections,* and if future investigations should show that through some idiosyncrasy on the part of the patient death *ever* is attributable to the injection of the serum, this would probably count for about as much as the rare deaths from the use of ether or chloroform.

The later reports show in general a decided improvement in the results of the treatment over the earlier ones, and there is every reason to believe that the results of the second year's employment of the new treatment will make a much more favorable showing than those of the first year. We shall come to a clearer understanding of the mode of action of the healing serum. Improvements in the methods of preparation and preservation of the serum, and possibly the separation of the healing substance, at least from other ingredients which produce the undesired effects, may be expected.

The discovery of the healing serum is entirely the result of laboratory work. It is an outcome of the studies of immunity. In no sense was the discovery an accidental one. Every step leading to it can be traced, and every step was taken with a definite purpose and to solve a definite problem."

The following tabulation, compiled largely from reports in *The Medical News*, for 1894 and 1895, and *Bulletin of Johns Hopkins Hospital*, July-August, 1895, shows a list of reported cases treated with diphtheria antitoxin, and speaks conclusively for the result. The hospital statistics everywhere show a surprising diminution of deaths since the introduction of the diphtheria antitoxic serum.

*This would seem to be at least a moderate estimate, as writing November 20th, 1894, Behring says that there had been up to that date certainly over 40,000 injections [(Das neue Diphtheriemittel, von Dr. Behring, Berlin, 1894, p. 25).

Report of Diphtheria Cases Treated with Antitoxin.

(With Report of Previous Fatality Treated by Ordinary Methods.)

Reporter.	Cases.	Deaths	Present Fatality. Per Cent.	Previous Fatality. Per Cent.	References.
Behring & Kossel....	117	13	11.1	58	Deut. med. Woch., p. 946.
Ehrlich & Wasserman	230	66	28.7	51	<i>Ibid.</i> , No. 16, xciv.
Martin & Chaillon....	300	78	26	50	Annales de l'Inst. Past., Sept., 1894.
Sonnenberg.....	107	22	20.5	27.6	Deut. med. Woch., 1894, No. 50.
Hahn.....	205	49	23.9	41	<i>Ibid.</i> , 1895, Verlius-Beilage, p. 2.
Weilger.....	63	18	28.5	39.8	La Méd. Mod., 1894, No. 85.
Baginsky	525	83	15.8	41.3	Serumtherapie der Diphtheriæ, Bagin- sky, Berlin, 1895.
Aronson	192	26	13.6	48	La Méd. Mod. 1894, No. 85.
Heubner.....	207	23	11.1	50	Münch. med. Woch., April 9, 1895.
Ehrlich.....	88	10	11.3	43	Med. Press and Circ., No. 2894.
Rumpf	36	2	5.5	39	Münch. med. Woch., 1894, No. 47.
Hilbert	11	0	0	37	Deut. med. Woch., 1894, No. 48.
Hager	25	1	4	38	Centralblatt für innere med., '94, No. 48.
v. Widerhofer	300	71	23.6	50	Münch. med. Woch., April 9, 1895.
v. Ranke.....	96	19	19.7	53	<i>Ibid.</i>
Stintzing	59	12	20.3	25	<i>Ibid.</i>
Rauchfuss.....	100	34	34	55	Deut. med. Woch., 1894, No. 48.
v. Mering.....	74	4	5.4	30	<i>Ibid.</i>
v. Noorden	81	19	23.4	45	British Med. Journal, No. 1767.
Schröder.....	63	8	12.7	35	<i>Ibid.</i>
Körte.....	121	40	33.1	53	Berlin klin. Woch., 1894, No. 46.
Börger.....	30	2	6.6	38	Deut. med. Woch., 1894, No. 48.
Ganghofner	110	14	12.7	39.5	Prague med. Woch., 1895, Nos. 1, 2, 3.
Carried forward..	3140	614			

REPORT OF DIPHTHERIA CASES.—Continued.

Reporter.	Cases.	Deaths.	Present Fatality.	Previous Fatality.	References.
Brought forward.	3140	614	Per Cent.	Per Cent.	
Roux.....	448	109	24.3	54	British Med. Journal, No. 1767.
Haudler.....	32	5	15.6	41	Wiener med. Presse, No. 6.
Hall.....	11	3	27.2	31.25	<i>Ibid.</i> , Jan. 19, 1895.
Tirard & Willcox.....	10	1	10	38	The Lancet, Jan. 19, 1895.
Lebreton.....	242	28	11.5	La Méd. Mod., 1894, No. 100.
Gougenheim.....	125	12	9.6	23.4	Annal. des Mal. de l'Oreille du Larynx et cet., 1895, No. 5.
Simon.....	16	2	12.5	La Méd. Mod., Feb. 6, 1895.
Ruffer.....	274	37	13.5	Brit. Med. Journal, Feb. 2, 1895.
Kossel.....	117	13	11.1	Deut. med. Woch., 1894, No. 15.
Epidemic in Trieste..	72	5	6.9	53
Cases in Hospital...	180	40	22.2	48	Das Oesterreich. Sanitätsw., Jan. 3, 1895.
Dreyfus.....	78	15	19.2	38	Lyon Médical, 1895, No. 5.
Rapmund.....	100	7	7	25	Zeitschrift f. med. Beante, Feb. 15, 1895.
Blumenfeld.....	50	2	4	Wiener klin. Woch., 1895, No. 3.
Schüller.....	32	1	3.1	Allgem. med. Cent. Zeitung, 1895, No. 88
Witthauer.....	36	5	13.9	Therapeut. Monatshefte, Feb., 1895.
MacCombie.....	31	4	12.9	Brit. Med. Journal, No. 1774.
Caiger.....	30	8	26.6	<i>Ibid.</i> , No. 1774.
Herringham.....	18	3	16.6	<i>Ibid.</i> , No. 1773.
Malvoz.....	15	1	6.6	Le Scalpel, Feb. 17, 1895.
Grünfeld.....	12	1	8.3	Abst. Schmidt's Jahrbüch, 1895, No. 10.
Saw.....	6	1	16.6	Lancet, 1894, No. 3711.
Schaerven.....	15	0	0	Berlin klin. Woch., 1895, No. 10.
Washbourne & Goodale	72	14	19.4	Brit. Med. Journal, No. 1773.
Heidenhain.....	24	3	12.5	Berlin klin. Wochenschrift, 1895, No. 10.
Carried forward..	5186	934			

REPORT OF DIPHTHERIA CASES.—Continued.

Reporter.	Cases	Deaths	Present Fatality.	Previous Fatality.	References.
Brought forward.	5186	934	Per Cent.	Per Cent.	
Fischer.....	225	35	15.5	..	N. Y. Med. Record, April 6, 1895.
Rise ¹	114	9	7.9	Deut. med. Woch., 1895, No. 10.
Weiland ..	20	0	0
v. Engel.....	39	10	25.6	50	Prager med. Woch., 1895, No. 48.
Mya.....	17	2	11.8	Wiener med. Blätter, 1895, p. 760.
Biggs (N. Y. City)...	255	40	15.6	45	N. Y. Med. Record, April 20, 1895.
Vierardt	63	16	25.4	58	Deut. med. Woch., 1895, p. 169.
Moizard & Perregaux.	231	34	14.7	55	Jour. de méd. et de Chirurg., Dec. 15, 1894
Lebreton	258	31	12	50	Le Bull. Méd., 1895, No. 10.
Le Gendre.....	17	3	17.6	55	Bull. et Mem. de la Soc. Méd. des Hop. de Paris, Dec. 20, 1894.
Sevestre & Meslay....	150	15	10	56	Le Bull. Méd., 1895, No. 18.
Saltman ..	89	13	14.6	27.2	Deut. med. Woch., 1895, No. 4.
Rosenthal.....	78	2	2.5	Trans. Phila. Co. Med., Sept. 11, 1895.
Snively....	8	0	0	<i>Ibid.</i>
Hauck, E. F. & L ..	49	4	8.1	<i>Ibid.</i>
Farrand	9	0	0	<i>Ibid.</i>
Bokai.....	176	42	23.3	59	Deut. med. Woch., 1895, No. 15.
Virchow	303	40	13.2	51.2	Münch. med. Woch., 1894, No. 50.
Escherich..	51	5	9.8	42	<i>Ibid.</i> , 1895, No. 7.
v. Muralt.....	58	2	3.4	0	Correspond. f. Schweizer-Aertze, '95, No. 5
Willard Parker Hosp	164	45	27.4	32.5
Cases in Cartagena .	156	21	13.4	0	British Med. Journal, July 6, 1895.
Lennox Browne.	45	2	4.4	34	Le Bull. Méd., 1895, No. 21.
Winkfield.....	22	4	18.1	36	British Med. Journal, May 11, 1895.
Blattner.....	38	9	23.7	Münch. med. Woch., March 5, 1895.
Carried forward..	7821	1318			

REPORT OF DIPHTHERIA CASES.—Continued.

Reporter.	Cases.	Deaths	Present Fatality.	Previous Fatality	References.
Brought forward..	7821	1318	Per Cent	Per Cent.	
Gerloczy.....	55	15	27.2	Münch. med. Woch., March 5, 1895.
D'Espine.....	60	6	10	Rev. Méd. de la Suisse Rom., April 20, '95.
Mason.....	306	81	26.4	49	Medical News, June 15, 1895.
Horowitz.....	21	1	4.8	20 7	Münch. med. Woch., June 11, 1895.
Van Nes.....	52	12	23.1	42	Deut. med. Woch., July 11, 1895.
Kuntzer.....	25	3	12	<i>Ibid.</i> , 1894, No. 49.
Schmidt....	14	3	21.4	<i>Ibid.</i> , 1894, No. 52.
Seiz.....	27	1	3.7	30.6	Therapeut. Monatshefte, Dec., 1894
Monti.....	25	1	4	29.8	Wiener med. Woch., 1895, Nos. 4 and 5.
Heim.....	27	6	22.2	52.5	<i>Ibid.</i> , 1895, No. 4.
Unterholzner.....	31	8	25.7	66 7	<i>Ibid.</i>
Bäumler.....	26	2	7.7	48	Münch. med. Woch., 1894, p. 1062.
Seitz.....	35	2	5.7	51	<i>Ibid.</i> , 1895, No. 12.
Moisard.....	248	34	13.7	47	Le Merc. Méd., 1894, No. 50.
Pavlik.....	13	1	7.6	Wiener med. Presse, 1895, Nos. 1 and 5.
Timmer.....	31	6	19.3	Deut. Med. Zeitung, June 10, 1895.
Howard.....	40	3	7.5	Medical News, June 1, 1895.
Kurth.....	97	10	10.3	Deut. med. Woch., July 11, 1895
Sigel.....	100	12	12	45	Münch. med. Woch., June 11, 1895.
Leichenst'rn&Wendel.	123	25	20.3	<i>Ibid.</i>
Brewer.....	6	0	0	Medical News, No. 1149.
Kub.....	5	1	20	<i>Ibid.</i> , No. 1150.
Welch.....	5	2	40	<i>Ibid.</i> , Nov. 17 and Dec. 1, 1894.
Fisher.....	34	2	5.9	Am. Journal of Med. Sci., No. 273.
Brown.....	40	2	5	Medical Record, April 27, 1895.
Gerhard.....	5	0	0	Codex Medicus, Aug., 1895.
Carried forward...	9272	1557			

REPORT OF DIPHTHERIA CASES.—*Continued.*

Reporter.	Cases.	Deaths.	Present Fatality.	Previous Fatality.	References.
Brought forward..	9272	1557	Per Cent.	Per Cent.	
Johnson & Roos.....	29	1	3.4	Report Phila. Co. Med. Soc., Sept. 11, '95.
Adams & Long.....	5	1	20	<i>Ibid.</i>
Hyde & Struble.....	18	2	11.1	<i>Ibid.</i>
Freund & Spivak.....	8	1	12.5	<i>Ibid.</i>
Muehleck.....	26	3	11.5	<i>Ibid.</i>
Wolff & Miller.....	23	0	0	<i>Ibid.</i>
Ebright.....	34	2	5.8	
Bennet.....	72	4	5.5	
Total.....	9487	1571			

The 9,487 cases reported show a death rate of only 16.5 *per cent.* where Antitoxic Serum has been employed, while under old methods the death rate was 47.5.

Where previous fatality is not tabulated it was not given by reporter.

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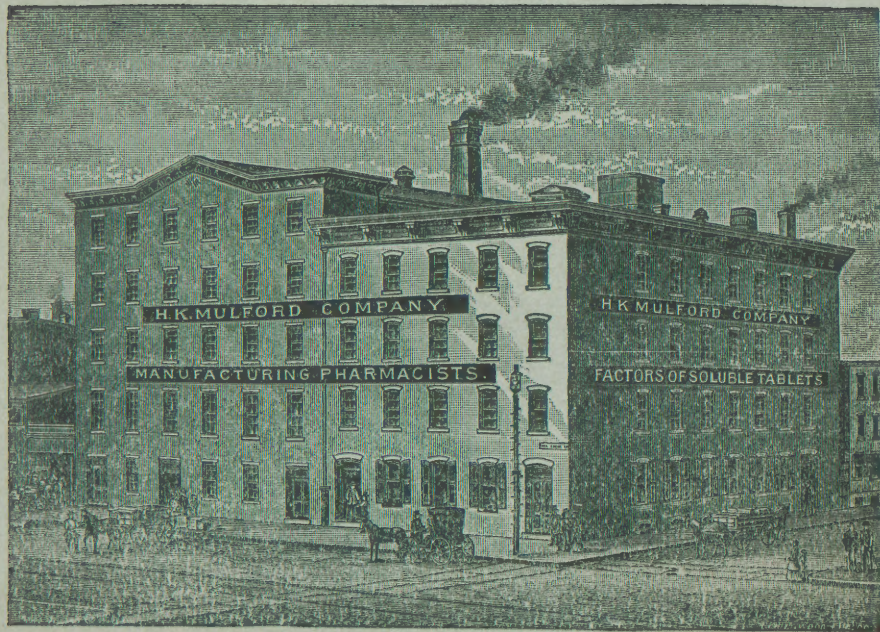
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